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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 18

Application Number: 09/840,746
Filing Date: April 23, 2001
Appellant(s): CHEN ET AL.

David G. Streeter
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/28/03.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

Issue 4 , claims 1, 3-6, concerning whether or not that the encoded protein is similarly expressed as the encoding polynucleotide of SEQ ID NO:2, has been withdrawn.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together as to Issue 4 is not agreed with because Issue 4 has been withdrawn.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Ausubel et al (eds). Current protocols in molecular biology (John Wiley & Sons, New York), 1987, p. 5.8.1

Bowie, J.U. et al. "Deciphering the message in protein sequences: Tolerance to amino acid subsstitutions". Science, vol.257 (March 16, 1990), pp. 1306-1310.

Bork, P. "Powers and pitfalls in sequence analysis: The 70% hurdle". Genome Research, vol. 10 (2000), pp. 398-400.

Burgess, W.H. "Possible dissociation of the heparin-binding and mitogenic activities of Heparin-binding (Acidic fibroblast) growth factor-1 from its receptor-binding activities by site-directed mutagenesis of a single Lysine residue". The Journal of Cell Biology, vol. 111 (1990), pp. 2129-2138.

Dermer G.B. "Another anniversary for the war on cancer". Bio/Technology, vol. 12 (1994), p:320

Drexler H.G. "Recent results on the biology of Hodgkin and Reed-Sternerg cells. II. Continuous cell lines". Leukemia and Lymphoma, vol.9 (1993), pp.1-25.

Embleton M. J. "Monoclonal antibodies to osteogenic sarcoma antigens". In: Wright, Jr. G.L. (ed). "Monoclonal antibodies and cancer". Immunol Ser, vol. 23 (1984) pp.181-207.

Freshney R. I (ed). Culture of Animal Cells, A Manual of Basic Technique, (Alan R. Liss, Inc, New York), 1983, p.4

Gillies, S.D. et al. « Antigen binding and biological activities of engineered mutant chimeric antibodies with human tumor specificities". Human Antibodies and Hybridomas, vol. 1, no. 1 (1990), pp. 47-54.

Hsu, T.C. « Karyology of cells in culture". In: Kruse et al (ed). Tissue Culture Methods and Applications (Academic Press, NY), 1973, pp. 764-767.

Lazar, E. et al. « Transforming growth factor alpha : Mutation of Aspartic acid 47 and Leucine 48 results in different biological activities". Molecular and Cellular Biology, vol. 8, no. 3 (March 1988), pp.1247-1252.

Ozen M. et al, "Establishment of an in vitro cell model system to study human prostate carcinogenesis: Involvement of chromosome 5 in early stages of neoplastic transformation". Intl J Oncology, vol. 8, no. 5 (1996), pp. 883-888

Rieger, A et al. In « Glossary of Genetics and Cytogenetics, Classical and Molecular", 4th edition, 1976, Springer-Verlag, New York, pp. 17-18.

Scott, D.A et al. « The Pendred syndrome gene encodes a chloride-iodide transport protein". Nature Genetics, vol. 21 (April 1999), pp. 440-443.

Sambrook et al (eds). Molecular cloning, a Laboratory manuall, 2nd ed, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY), 1989, p.8.3-8.7.

Tao, M.H. et al. « Studies of aglycosylated chimeric mouse-human IgG. Role of carbohydrate in the structure and effector functions mediated by the human IgG

constant region". The Journal of Immunology, vol. 143, no. 8 (October 15, 1989), pp. 2595-2601.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

REJECTION UNDER 35 USC 101, UTILITY

35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility.

Claims 1-6 are drawn to 1) the nucleic acid sequence of SEQ ID NO:2, or a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:1, or complement thereof, or a naturally occurring variant of SEQ ID NO:2 having at least 90% sequence identity with SEQ ID NO:2 or the complement thereof, 2) a composition comprising said nucleic acid sequence and a labeling moiety, 3) a vector comprising said nucleic acid sequence, a host cell comprising said vector, and 4) a method for using a cDNA to produce a protein.

The disclosed utilities for SEQ ID NO:2 or MRTM (mucine related tumor marker) include diagnosis and treatment of cancer, in particular breast cancer, production of and screening of antibodies that specifically bind to SEQ ID NO:2 (p.16-23). However, neither the specification nor any art of record teaches what SEQ ID NO:2 is, what it does do, they do not teach a utility for any of the variants claimed, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. Therefore, the claimed polynucleotides lack specific and established utility.

The asserted utilities for SEQ ID NO:2, such as production of and screening of agonists, antibodies and antagonists apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to SEQ ID NO:2. Additional disclosed utilities for SEQ ID NO:2 include therapy and diagnosis of cancer, in particular breast cancer. The asserted utility of SEQ ID NO:2 is based on the assertion that SEQ ID NO:1, encoded by SEQ ID NO:2 has chemical and structural homology to mucin proteins, and that in particular SEQ ID NO:1 and human mucin MUC3 and porcine gastric mucine PGM-9B share 26% identity (p.10, second paragraph bridging p. 11 and figure 2). In addition, SEQ ID NO:1 has a biologically active portion extending from C594 to C627. Further, SEQ ID NO:1 has 13 potential N-glycosylation sites, several potential phosphorylation sites, one potential aspartic acid and asparagines hydroxylation iste, one potential EGF-1-like domain signature, one potential EGF-2-like domain signature, two potential calcium-binding EGF-like domain signatures, and a predicted transmembrane segment (p.10). By

Northern analysis, SEQ ID NO:2 is overexpressed in breast cancer cell line BT20 as compared to normal cells (table 1 on p.40). The specification discloses that cell lines derived from human mammary epithelial cells at various stages of breast cancer provide a useful model to study the process of malignant transformation and tumor progression, as it has been shown by Wistuba et al, 1998, Clinical Cancer Res, 4: 2931-2938, that these cell lines retain many of the properties of their parental tumors for lengthy culture periods (specification, p.2, paragraph before last).

It is noted that the specification does not disclose any biological activity of SEQ ID NO:1, nor any data confirming that the portion extending from C594 to C627 of SEQ ID NO:1 has any biological activity, nor consensus sequences required for the activity of the encoded protein or for the identification of a mucin protein. It is clear that, although there is a 26% identity between human mucin MUC3 and porcine gastric mucine PGM-9B and SEQ ID NO:1, there is a 74% dissimilarity between SEQ ID NO:1 and human mucin MUC3 and porcine gastric mucine PGM-9B; and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in

any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al, who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 74% dissimilarity to human mucin MUC3 and porcine gastric mucine PGM-9B, the function of the SEQ ID NO:1 could not be predicted, based on sequence similarity with human mucin MUC3 and porcine gastric mucine PGM-9B, nor would it be expected to be the same as that of human mucin MUC3 and porcine gastric mucine PGM-9B In addition, Bork clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398,

col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrogngly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Further, Scott et al teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat

sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter downregulated in adenoma. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Clearly, given not only the teachings of Bowie et al, Lazar et al, Burgess et al and Scott et al, but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 74% dissimilarity to human mucin MUC3 and porcine gastric mucine PGM-9B, the function of the SEQ ID NO:1 could not be predicted, based on sequence similarity with human mucin MUC3 and porcine gastric mucine PGM-9B, nor would it be expected to be the same as that of human mucin MUC3 and porcine gastric mucine PGM-9B. Further, even if SEQ ID NO:1 is a human mucin MUC3 and porcine gastric mucine PGM-9B -like protein, neither the specification nor any art of record teaches what the polypeptide is, what it does, does not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active or which derivatives would function as claimed in a pharmaceutical composition.

Because of this, the claimed polynucleotides lack substantial utility, and further experimentation is required to determine what use is for the claimed polynucleotides.

Moreover, although the specification discloses overexpression of SEQ ID NO:2 in a breast cancer cell line BT20 as compared to normal cells, and although Wistuba et al teach that cell lines recited in table 2 on page 2936 retain many of the properties of their parental tumors for culture periods up to 60 months, the cell lines studied by Wistuba et al are specific cell lines that are cultured from a subset of primary breast carcinomas that have several features indicative of advanced tumors with poor prognosis, whereas it seems that the cell line BT20 studied in the claimed invention is not from the same subset of primary breast carcinoma and is not the same as the cell lines studied by Wistuba et al. Thus it is unpredictable that the cell line BT20 has any of the properties of the cell lines studied by Wistuba et al, and retain many of the properties of their parental tumors for culture periods up to 60 months. Further, the period of culture of the cell lines studied by Wistuba et al during which the retention of the parental tumors are retained is only up to 60 months. It is not clear how long the cell line BT20 has been in culture, especially it is well known in the art that cell lines could have been in culture for years and years.

In addition, it is well known in the art that characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor, and that acquisition or loss of certain properties, or change in chromosome constitution of cells in culture frequently occurs during adaptation to culture system, and further that only a few cell lines contain cells that resemble the in vivo cancer cells. Drexler et al specifically

teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Ozen et al teach that prostate cells in late culture all show numerous changes in chromosome 5 in addition to some new markers. The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment

lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the cell culture data presented in the specification, it could not be predicted that the cell line BT20 could represent the parental breast cancer, and that overexpression of SEQ ID NO:2 in the cell line BT20 could be correlated with overexpression of SEQ ID NO:2 in primary breast cancers. Because of this, the claimed polynucleotides lack specific utility, and further experimentation is required to determine what use is for the claimed polynucleotides.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a specific, substantial asserted utility or well established utility for the reasons set forth, credibility of any utility cannot be assessed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The following is a quotation of the first paragraph of 35 USC 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the written description inquiry, *whatever is now claimed*. (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Claims 1-6 are drawn to 1) the nucleic acid sequence of SEQ ID NO:2, or a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:1, or "complement" thereof, or a "naturally occurring variant of SEQ ID NO:2 having at least 90% sequence identity with SEQ ID NO:2" or the "complement "thereof, 2) a composition comprising said nucleic acid sequence or the complement thereof and a labeling moiety, 3) a vector comprising said nucleic acid sequence, a host cell comprising said vector, and 4) a method for using a cDNA to produce a protein.

It is noted that a complement could be partial or complete complement, wherein partial complement could share with SEQ ID NO:2 only a few common nucleotides.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the written description inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:16, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that An adequate written description of a DNA... requires a precise definition, such as by structure, formula, chemical name, or physical properties , not a mere wish or plan for obtaining the claimed chemical invention .

Support for allelic variants is provided in the specification on page 9, lines 13-9, where it is disclosed that the invention encompasses allelic variants that have high percent identity with SEQ ID NO:2, and may differ by about three bases per hundred base, and on page 11, wherein it is disclosed that the invention encompasses variants having at least 80%, 90% or 95 % identity to SEQ ID NO:2. This is insufficient to support the generic claims as provided by the Interim Written Description Guildlines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

The instant specification fails to provide sufficient descriptive information, such as definitive strutural or functional features of the claimed genus of polynucleotides.

The claims read on polynucleotide variants of SEQ ID NO:2, wherein said variants have any type of substitution besides conservative substitution, at any amino

acid, throughout the length of the nucleic acid or polypeptide, as well as insertions and deletions, provided that the resulted variation is up to 10% difference with SEQ ID NO:2. The specification and the claims do not place any limit on which amino acid that is subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous structural polynucleotide variants, and nucleotide sequences encoding numerous structural variants. The specification and the claims do not provide any guidance as to which, or how many original amino acid(s) that are naturally substituted, or to which type of substitution besides conservative substitution, or which amino acids that are naturally deleted or inserted so that the claimed polypeptide could function as contemplated. Structural features, that could distinguish the claimed structural polynucleotide variants and nucleotide sequences encoding the polypeptide variants from the nucleotide sequences known in the art, are missing from the disclosure. No common structural attributes that identify the claimed structural polynucleotide variants and nucleotide sequences encoding the polypeptide variants are disclosed. In addition, no common functional attributes that identify the claimed structural polynucleotide variants and nucleotide sequences encoding the polypeptide variants are disclosed, because the function of a nucleotide sequence could be abolished, even with substitution of only one amino acid of the peptide encoded by said nucleotide sequence (Burgess et al).

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the

disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Therefore only an isolated DNA molecule comprising a DNA sequence comprising SEQ ID NO:2, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

If Appellants could overcome the above 101 and 112, first paragraph rejection, claims 1-6 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2, does not reasonably provide enablement for variants of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Appellants have not shown how to make and use the claimed variant polynucleotides, and nucleotide sequences encoding the polypeptide variants which are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Such unpredictability would equally apply to DNA sequences which encode proteins. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al). In

transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al., and Gillies et al.). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to make and use the claimed invention as broadly as claimed.

(11) Response to Argument

REJECTION UNDER 35 USC 101, UTILITY

Rejection under 35 USC 101 of claims 1-6 pertaining to lack of a specific and substantial asserted utility or a well established utility remains for reasons already of record .

Appellant asserts on pages 4-6 in the response that the claims have patentable utility and a well known utility. Appellant asserts that the claimed polynucleotide codes for a polypeptide demonstrated to be a member of the class of mucin proteins, which has provided valuable tumor markers for clinical diagnosis of cancer. Appellant asserts that the claimed polynucleotide has numerous practical,

beneficial uses in toxicology testing, drug development and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions.

Appellant recites the Declaration of Bedilion, which describes how the claimed polynucleotide can be used in gene expression monitoring applications, well-known in the art, and how those applications are useful in developing and monitoring their activity, and which states that the claimed inventnioon is a useful tool when employed as a highly specific probe in a cDNA microarray.

Appellant asserts that the Examiner contends that the claimed polynucleotide cannot be useful without precises knowledge of its biological function, that that the law has never require knowledge of biological function to prove utility.

This is not found to be persuasive. The polypeptide encoded by the claimed polynucleotide has not been shown to be a member of the class of mucin proteins, because based on sequence similarity with mucin proteins, one cannot predict that the polypeptide encoded by the claimed polynucleotide is a member of the class of mucin proteins, based on the teaching of Bowie et al, Lazar et al, Burgess et al, and Scott et al that function of a protein cannot be predicted based solely on sequence similarity.

Further, one cannot make a meaningful interpretation of the information obtained from the microarray about the specific nucleic acid molecule because the skilled artisan has no information regarding the significance of this molecule. Without knowing what biological processes are mediated by the claimed nucleic acid molecule, the skilled artisan would not be able to evaluate the results of the microarray for a toxic response

or a beneficial response. Further, one cannot determine whether the putative overexpression of the claimed polynucleotide in the breast cell line BT20 compared to normal cell lines, as detected by microarray, is not due to instability of expression of genes of cells cell culture, based on the teaching of Drexler et al, Embleton et al, Hsu, Mustafa Ozen et al, Freshney, and Dermer that acquisition or loss of certain properties, or change in chromosome constitution of cells in culture frequently occurs during adaptation to culture system, and that only a few cell lines contain cells that resemble the in vivo cancer cells.

I. The Applicable Legal Standard

Appellant summarizes case law on the utility requirement at pages 6-7 in the response.

II. Toxicology testing, drug discovery and disease diagnosis

Appellant argues at pages 8-13 in the brief that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of diseases and that these uses are "well-established" and confer "specific benefits' to the public.

Beginning at p. 5, second paragraph, Appellant discusses the Bedilion declaration. Appellant recites that the Declaration by Dr. Tod Bedilion describes the use of the claimed polynucleotides in microarray of the type first developed at Standford University for gene expression monitoring, for evaluating the efficacy and toxicity of drugs, and thus useful in developing drugs and monitoring their activity.

Appellant characterizes the Bedilion declaration as describing some of the practical uses of the claimed invention in gene and protein expression monitoring

applications, thus allegedly demonstrating the examiner's position to be without merit. In particular, Appellant states that the Bedilion declaration describes how the claimed expressed polynucleotide can be used in gene expression monitoring systems that were well-known at the time of the invention, and how those applications are useful in developing drugs and monitoring their activity. Appellant quotes from the Bedilion declaration, that states that microarrays containing SEQ ID NO: 1-encoding polynucleotides would be a more useful tool than microarrays lacking same in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative and developmental disorders for such purposes as evaluating their efficacy and toxicity.

This is not found to be persuasive. As an aside, it is noted that Dr. Bedilion is a consultant for Incyte Pharmaceuticals, Inc., the real party in interest in this appeal, and thus is a concerned party. Regarding the merit of the argument, any new polynucleotide can be used in a microarray, and thus this asserted utility is not specific. Also, the disclosure that the polypeptide encoded by the claimed polynucleotide is structurally related to mucin genes, and that the claimed polynucleotide is overexpressed in breast cell line BT20 in culture does not render the asserted utility specific, since the specification does not establish that the claimed polynucleotide is expressed in any diseased tissues in any way that is different from the way it is expressed in healthy forms of the same tissues. In other words, the specification does not disclose that the claimed polynucleotide is expressed in tissues having cell proliferative or developmental disorders at altered levels or in variant forms. Thus, it is

not a target for drug development, toxicology studies, or disease diagnosis. Significant further research would have to be conducted to identify diseases states which correlate with altered levels or forms of the claimed polynucleotide. Therefore, this asserted utility is also not substantial.

The Bedilion Declaration cites 11 separate references with regard to the state of the art with regard to microarrays at the time of the invention (paragraph 7). The Examiner concedes that microarray technology was known in the art at the time of the instant invention. In paragraph 10 of the Declaration, Dr. Bedilion states "persons skilled in the art at the time the invention was filed clearly would have understood the Chen 746' application to disclose the SEQ ID NO:2 polynucleotide to be useful in cDNA microarrays for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity". This paragraph continues on page 7; "[t]he ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process". However, without knowing what biological processes are mediated by the claimed nucleic acid molecule, the skilled artisan would not be able to evaluate the results of the microarray for a toxic response or a beneficial response. For example, the expression level of the claimed nucleic acid goes up significantly, while the expression patterns of known tumor inducers goes down. Is this good or bad?? One may conclude that this is a bad result, however, if the claimed nucleic acid molecule

encodes a tumor suppressor, this would be good. One cannot make a meaningful interpretation of the information obtained from the microarray about the specific nucleic acid molecule because the skilled artisan has no information regarding the significance of this molecule.

In paragraph 11 of the Declaration, the Schena reference is cited. However, as stated in Schena et al. (Science. 270: 467-470, 1995 at page 469, column 3, paragraph 3) "[a] wide variety of acute and chronic physiological and pathological conditions might lead to characteristic changes in the patterns of gene expression in peripheral blood cells or other easily sampled tissues. In concert with cDNA microarrays for monitoring complex expression patterns, these tissues might therefore serve as sensitive in vivo sensors for clinical diagnosis." Therefore, it is the pattern of the microarray, containing hundreds or thousands of pieces of DNA, which provides information regarding disease states and clinical diagnosis, and not an individual piece of DNA. The microarray does not rely on the specifics of the elements which make up the microarray, but rather, the collection of the pieces. In this regard, the use of any particular DNA is not specific, since any collection of DNA would be useful. The change in the expression level of a particular DNA, such as that claimed in the instant application, does not provide useful information regarding disease state because there has been no correlation or nexus established between the claimed nucleic acid and any disease condition. Therefore, this utility is not substantial since there is no immediate benefit to the public.

Paragraph 12 of the Declaration references two patents (Shalon and Brown), however, their disclosures do not speak to the invention which is claimed, which is the

nucleic acid molecule of SEQ ID NO:2. The two references are directed to microarray technology in general.

Paragraph 13 of the Declaration references the DeRisi article, but again, this reference is not on point with the claimed invention, but discusses uses of microarrays for studying gene expression patterns in cancer. However, it would appear that the pattern of the array is what is used for diagnosing the cancer, and knowledge of the specific genes in the array is necessary for identifying targets for therapeutic intervention (see page 458, column 2, paragraph 2).

Paragraph 14 of the Declaration discusses the Shalon and Heller references. However, Heller et al. (Proc. Natl. Acad. Sci. USA 94; 2150-2155, 1997 at page 2155, column 1, final paragraph) indicate that microarrays are suited for profiling disease and for identifying related genes and that microarrays "could provide new targets for drug development and disease therapies". Therefore, again it is the results of the microarray which will determine if the nucleic acid molecule used in the array is a target for drug development, and not the fact that the nucleic acid could be used in the microarray alone which dictates this fate. It is the result of the microarray which will indicate that a gene is related to a disease, and therefore, has the utility of being useful in diagnosis and treatment. However, prior to this experimentation, there is no indication of a specific, substantial and credible utility for the invention as claimed.

In paragraph 15 of the Declaration, the Bedilion Declaration concludes that "the Chen 746' application would have led a person skilled in the art at the time it was filed, who was using gene expression monitoring in connection with working on developing

new drugs for the treatment of cancer to conclude that a cDNA microarray that contained the SEQ ID NO:1 encoding polynucleotide would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes to contain the SEQ ID NO:1 encoding polynucleotide". This conclusion is not based on any facts of record. There is no evidence in the instant specification that correlates or provides a nexus with the claimed nucleic acid and cancer. It is clear that the claimed nucleic acid was overexpressed in a breast cancer cell line, BT20, but there is no indication that it was overexpressed in breast cancer tissue. The overexpression of the claimed nucleic acid in a breast cancer cell line, BT20, could be due to cell culture artifacts and is not related in any way to breast cancer. To conclude that cancer treating drugs could be evaluated for their efficacy and toxicity using the nucleic acid of SEQ ID NO:2 is premature and not supported by any facts of record. Lack of knowledge of the biological significance of SEQ ID NO:2 in cancer, if any role exists, precludes one skilled in the art from evaluating any data obtained from the microarray as it pertains to the expression of SEQ ID NO:2. If the nucleic acid molecule of SEQ ID NO:2 has no relation to cancer, and its expression level is increased, this provides no information regarding efficacy and no useful information regarding toxicity for the tested drug, absent evidence to the contrary.

In section (e) of paragraph 15 of the Declaration, Dr. Bedilion concludes that in view that SEQ ID NO:2 polynucleotide is isolated from a lung cDNA library, and that microarray experiments show the differential expression of SEQ ID NO:2 (MRMT) in human breast adenocarcinoma cells BT20, persons skilled in the art at the time the

invention was filed would have considered SEQ ID NO:2 to be an important and valuable addition to a cDNA microarry for use in cancer research. However, as stated previously, the results obtained from the microarray would not provide immediately useful information regarding the diagnosis and treatment of cancer without the prior knowledge of a correlation or nexus with cancer, or the specific role the claimed nucleic acid molecule in cancer. Therefore, use of the claimed nucleic acid molecule in such a microarray would be to use it as an object of further research, which is not a substantial utility.

Paragraph 16 of the Declaration states that the claimed nucleic acid molecules could be used as probes in (a) northern analysis, (b) expression profiling , (c) as a standard in hybridization assays, or (d) tissue or cell typing. However, each of these uses do not appear to be specific, since any nucleic acid could be used in these methods and the particulars of the claimed nucleic acid molecule are not disclosed.

Appellants discuss at page 8-9 of the Brief the Bedilion declaration's detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations. Appellant points to Dr. Bedilion's pages of text and numerous subparts explaining the importance of this technology. Appellant points to Dr. Bedilion's explanation that those skilled in the art at the time of the invention without any doubt would have appreciated the criticality of toxicity testing.

The argument is not found to be persuasive. There is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing. However, the claims are not

drawn to the technique. The claims are directed to polynucleotides which have not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Any such polynucleotide could be added to a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial.

Appellant urges that the Bedilion declaration establishes that persons skilled in the art, guided by the instant specification, at the time of the invention would have wanted their cDNA microarrays to comprise the claimed polynucleotide, because a microarray comprising the claimed polynucleotide would provide more useful results in the kind of gene expression monitoring studies that microarrays lacking the claimed polynucleotide. This is not found to be persuasive. The specification has not linked the claimed polynucleotide with any specific disease state or disorder, as discussed above and in previous Office Actions. Adding the claimed polynucleotide to a microarray would not make the microarray any more valuable than adding any other "orphan" polynucleotide. The asserted utility is not specific to the claimed polynucleotide.

At page 10 of the Brief (second paragraph), Appellants argue that the examiner does not address the fact that, as described on page 14 of the specification, the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotides. Appellants conclude that the claimed invention is not, in that

regard, some random sequence whose value as a probe is speculative or would require further research to determine.

This is not found to be persuasive. Any polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it. However, unless the significance of detecting the mRNA is known, because of some correlation between its expression and a condition or illness or function, then the use of a nucleic acid to probe for such expression constitutes at best, further research and not a substantial utility.

At page 10 of the brief, Appellants argue that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Appellants review case law pertinent to the patentable utility of research tools. This is not found to be persuasive.

Appellants' analogy is misplaced. It is true that a scale has patentable utility as a research tool. However, the object being weighed on the scale does not necessarily have patentable utility. In the instant case, microarray technology has patentable utility. However, the microarray is not being claimed, but rather a polynucleotide that can be used in microarrays. The claimed polynucleotide is not disclosed as being expressed at an altered level or form in any diseased tissue as compared to the corresponding healthy tissue. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or member of, a microarray is not specific. Any orphan polynucleotide can be used in the same way.

At page 10, last two pargraphs, bridging page 11 of the brief, Appellants refer to Dr. Bedilion's discussion of the Brown et al. Patent (U.S. 5807522), attached to the declaration. Dr. Bedilion characterizes the patent as providing evidence that microarrays can be used in numerous genetic applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins.

This is not found to be persuasive. The Brown patent claims methods of forming microarrays. Microarray methods have patentable utility as a research tool, just like a scale or a gas chromatograph. However, what the research tool measures does not necessarily have patentable utility, such as the object being weighed by the scale, or the compound being analyzed by the gas chromatograph. Such is the situation at issue.

At page 11 of the Brief, Appellants refer to other publications, that discuss microarrays and gene expression technology with respect to drug screening and toxicology testing. Again, this is not found to be persuasive, because the arguments and evidence merely show that microarray technology is important and useful to the scientific community. These publications do not show that the claimed invention has a patentable utility. The use of the claimed uncharacterized polynucleotides in such studies would have provided no more information than the use of any other orphan polynucleotide. The asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide. Due to the lack of disclosure of a correlation between the

claimed polynucleotides and a particular disorder, the asserted utility is also not substantial, as discussed above.

Appellant further asserts that use of proteins expressed by human as a tool for toxicology testing, drug discovery and diagnosis of disease is a well-established utility as confirmed by Rockett et al, Lashkari et al, and that the claimed polynucleotide could be used in array experiments to study the effect of toxicological compounds, as indicated in the email from Dr. C. Afshari to the undersigned. Appellant concludes that there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening, and that the claimed polynucleotides could be used in this manner.

The argument is not found to be persuasive, because for a utility to be "well-established" it must be specific, substantial and credible. In this case, as indicated by Appellant in the response, all nucleic acids and expressed genes are in some combination useful in toxicology testing, or useful as a tool for research. However, the particulars of toxicology testing with the claimed polynucleotide of SEQ ID NO:2 are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified from drug screening using microarrays. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to SEQ ID NO: 2. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet

been disclosed, the utility is not substantial because it is not currently available in practical form.

Moreover, use of the claimed polynucleotides in an array for toxicology screening or expression profiling is only useful in the sense that the information that is gained from the array or profile is dependent on the pattern derived from the array or profile, and says nothing with regard to each individual member of the array or profile. Again, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNAs. Even if the expression of Appellant's polynucleotides is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the claimed polynucleotides has no "well-established" use.

The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding the claimed polynucleotide and the encoded polypeptide could be put.

Appellant states on pages 13-14 in the response that potential benefits to the public is enormous. Appellant cites 1) CV Therapeutics uses Incyte gene expression to identify the key gene associated with Tangiers disease, 2) reduction of time associated with target discovery and validation by Incyte customers, and 3) over 50% of the drug targets in the pipeline of Incyte customer are from Incyte database.

This is not persuasive because this assertion fails to address the utility of the individually claimed polynucleotides encoding SEQ ID NO:1, or the encoded

polypeptide. Further, in the absence of any disclosed relationship between the claimed polynucleotide and the encoded polypeptide and any disease or disorder and the lack of any correlation between the claimed polynucleotide and the encoded polypeptide with any known disease or disorder, any information obtained from a screening assay would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPO at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

The question at issue is whether or not the broad general assertion that the claimed polypeptides might be used for *some* diagnostic application, *some* drug discovery or *some* toxicology test (in the absence of a disclosure of *which* diagnostic application, *which* drug discovery or *which* toxicology test) would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPO 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to

show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates').

Appellant asserts, at page 14 in the response, that the use of the claimed invention as a tool for toxicology testing is a practical, real world use and is a "substantial" use. Appellant asserts that there is a vibrant market for databases containing all expressed genes. Appellant asserts that as used in toxicology testing, drug discovery and disease diagnosis the claimed invention has a beneficial use in research other than studying the claimed invention itself.

This is not persuasive because the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner*, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed polynucleotide encoding SEQ ID NO:1 or the polypeptide encoded thereby has any utility.

III. The rejections are with merit

At pages 15-16 in the Brief, Appellant argues that the precise biological role or function of an expressed polynucleotide however is not required to demonstrate utility. Appellant asserts at page 16 of the Brief that knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit and criticizes the Examiner's position that the claimed polynucleotide cannot be useful without precise knowledge of its biological function.

Appellant is mischaracterizing the Examiner's position. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses a credible, specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed polynucleotide is expressed in colon cancer and not expressed in healthy colon tissue. The hypothetical specification does not disclose the biological activity of the polypeptide encoded by the polynucleotide. The claimed polynucleotide in the hypothetical example would not be rejected under 35 U.S.C. §§ 101 and 112, first paragraph, as it has utility and is enabled as a colon cancer marker. However, such is not the fact pattern here. Contrary to Appellant's assertion at page 15 of the Reply Brief, the Examiner has never required knowledge of biological function.

Appellant asserts, at pages 16-17 in the Brief, that the use of the claimed invention as a tool of research for toxicology testing and is a "substantial" use. Appellant asserts that as used in toxicology testing, drug discovery and disease diagnosis the claimed invention has a beneficial use in research beyond mere studying the claimed invention itself.

This is not persuasive. Appelant assertion of such use does not qualify as a patentable utility, because it is not specific to the claimed polynucleotide. Any polynucleotide that represent a sequence found in nature could be used as a tool for research in toxicology testing, drug discovery and disease diagnosis. Further, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological

screen(s) for which the claimed compounds would be useful. In *Brenner*, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPO at 690. Here, there is no evidence that the claimed polynucleotide encoding SEQ ID NO:1 or the polypeptide encoded thereby has any utility.

Appellant asserts on pages 17-18 that in addition to ignoring the specific and substantial utilities of the claimed invention in toxicology testing, the Examiner disputes Appellant's asserted utility based on differential expression of the claimed polynucleotide in breast cancer as determined by microarray. Appellant asserts that none of articles recited by the Examiner provide the basis for a sweeping conclusion that cell lines are generally recognized as unsuitable models for the study of human cancers. Appellant asserts that Wistuba et al reports the finding of 18 human breast cancer cell lines compared with their archival tumor tissues, and concludes that "thus, breast carcinoma cell lines are useful models for studying at least one major form of breast cancer" (bottom of page 2937).

Appellant asserts that the data in Table 1 is not derived from electronic Northern analysis, but from a microarray format. Appellant challenges the Examiner's contention that the cDNA databases, such as LIFESEQ database recited in the instant specification are underepresentative of actual expressed gene, because Appellant has provided a published article reciting that the most recent estimates of the human

genome projected approximately 30,000 genes, considerably less than the 100,000 figure provided by the Examiner.

This argument is not found to be persuasive. It is noted that although Wistuba et al teach that breast carcinoma cell lines are useful models for studying at least one major form of breast cancer, Wistuba et al do not teach that differential expression of genes in breast cancer cell lines would be useful as a marker for breast cancer. Further, although some of the breast cancer cell lines studied by Wistuba et al have correlation with their corresponding tumor tissue, concerning various criteria such as morphological features, presence of aneuploidy, immunohistochemical expression of estrogen receptors etc.., it seems that the cell lines studied by Wistuba et al are only from a specific subset of primary breast carcinoma. The breast cell line BT20 used in the claimed invention, however, seems not to be from the same subset of primary breast carcinoma taught by Wistuba et al. Further, the period of culture of the cell lines studied by Wistuba et al during which the retention of the parental tumors are retained is only up to 60 months. It is not clear how long the cell line BT20 has been in culture, especially it is well known in the art that cell lines could have been in culture for years and years. Further, there is a widespread belief in the scientific community that they are not representative of the tumors from which they were derived, due to extensive chromosomal rearrangements, oncogene mutations, and multiple sites of allelic loss and gene amplification in tumor cell lines, including breast carcinoma cell lines, as taught by Drexler et al, Embleton et al, Hsu et al, Ozen et al, Freshney et al, Dermer et al.

Thus, in view of of the above, it is unpredictable that the cell line BT20 has any of the properties of the cell lines studied by Wistuba et al, and retain many of the properties of their parental tumors, and one cannot determine whether that the putative overexpression of the claimed sequence in the breast cell line BT20 is not due to cell culture artifacts.

Moreover, it seems that the microarray used in the instant application for screening the overexpression of the claimed polynucleotide seems to be underrepresentative of all the mRNAs in the target cells, because the UNIGEM V microarray represents only 4610 annotated genes (specification, page 36, lines 20-21), which are far below the most recent estimates of the human genome projected approximately 30,000 genes, as recited by Appellant. Further, analysis of a microarray which is composed of cDNAs immobilized on glass slides (specification, page 36, lines 25-26) is similar to analysis of substractive cDNA libraries for screening overexpression of a gene, in that a microarray has to be representative of each mRNA in a cell. A complete cDNA library is one that contains at least one cDNA clone representing each mRNA in a cell, and that there are about 34,000 different types of mRNAs in a mammalian cells and about 500,000 mRNA molecules per cell, as taught in a commonly used text book by Ausubel et al, eds, 1987 (Current protocols in molecular biology, John Wiley & Sons, New York, p. 5.8.1, under Production of a cDNA library). Ausubel et al further teach that if the number of molecules of the rarest mRNA in a cell is 8, the calculated number of clones that should be screened to achieve a 99% probability that a cDNA will exist in the library is 324,000. Similarly, in another commonly used text book

by Sambrook et al, eds, 1989 (Molecular cloning, a Laboratory manuall, 2nd ed, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, p.8.3-8.7). Sambrook et al teach that a typical mammalian cell contains between 10,000 and 30,000 different mRNA sequences. Sambrook et al further teach that for low abundance mRNAs, i.e. 14 copies/cell, although the minimum clones required to obtain representation of mRNAs of this class is 37,000, but because of preferential cloning of certain sequences, a much larger number of recombinants must be obtained to increase the chances that any given clone will be represented in the library, i. e., about 170,000 clones (Sambrook et al, p.8.5 last paragraph, bridging p.8.7). Sambrook et al also teach that unfortunately, many mRNAs of interest are present at even lower level, i.e. 1 molecule/cell is not unusual. Thus based on the teaching in the art, it is clear that the microarray used in the claimed invention would not be representative of all mRNAs present in a cell. The fact that the claimed polynucleotide is not expressed in one set of microarray or is expressed in another appears to be an artifact of the analytical system and cannot be extrapolated to a prediction of whether that molecule is expressed in the tissue "represented" by the microarray. It is not possible to determine from the information in the specification whether SEQ ID NO:2 could be useful in cancer research or as a marker for cancer cells without further research on the material itself.

Appellant argues on pages 18-20 that the use of polynucleotides in microarrays is a patentable utility, even though they assert that it applies to all expressed genes, because there is no legal requirement that an invention's utility be "unique" to the

invention. Rather, Appellant argues, an invention can be a member of a class, where all the members of the class share a common utility.

First, Appellant's characterization of the Office's position is somewhat misleading. Appellant has never been asked to identify a utility that is unique, i.e., not shared by any other compounds or compositions. Rather, Appellant has been required to identify a utility that is specific to the invention claimed, as opposed to one that would apply regardless of the specific properties of the claimed invention. See, e.g., Brenner, 383 U.S. at 534, 148 USPQ at 695 (An invention does not have utility sufficient to satisfy § 101 until it is "refined and developed" to the point of providing a specific benefit in currently available form.).

An invention certainly can have a utility that is shared by other compounds or compositions. Take, for example, an application that claims ibuprofen and discloses that it is useful as an analgesic. No one would argue that a claim to ibuprofen lacks utility simply because aspirin and acetaminophen are also useful as analgesics. On the other hand, not every utility will satisfy § 101, even if the utility is shared by a class of inventions. Assume that the above-described application did not disclose that ibuprofen was an analgesic but only disclosed that it is useful because it can be used to fill a jar which would then be useful as a paperweight. There would be little doubt that this disclosed utility would not satisfy § 101, even though the utility is shared by a large class of inventions, viz., those whose physical embodiments have mass. So while a utility need not be unique to a claimed invention, it must nonetheless be specific, and in currently available form, in order to satisfy § 101.

Here, Appellant asserts that any expressed human gene or protein can be incorporated into a microarray, and that the microarray can then be used to monitor changes in expression of the genes represented therein. However, any observed results of changed expression of SEQ ID NO:1-encoding gene would have no meaning without additional knowledge of what a change in expression of SEQ ID NO:2 means. The specification in effect discloses that the claimed products can be put on microarrays, and those of skill in the art will figure out what to do with them. This utility is not substantial; it does not provide a specific benefit in currently available form. Appellant's position may be that a microarray has utility and a microarray is made up of thousands of genes or gene fragments; therefore, since the genes collectively provide the data generated by the micro array, each one of the genes represented in the microarray has utility. Assuming arguendo that a generic microarray – one comprising thousands of uncharacterized or semi-characterized gene fragments – would provide a useful tool for, e.g., drug discovery, it does not follow that each one of the genes represented in the microarray individually has patentable utility. Although each gene in the microarray contributes to the data generated by the microarray overall, the contribution of a single gene – its data point – is only a tiny contribution to the overall picture.

The Brenner Court held that § 101 sets more than a de minimis standard for utility. Therefore, the patentable utility of a microarray, for example, does not necessarily mean that each tiny component of the microarray also has patentable utility. A patentable utility divided by a thousand does not necessarily equal a thousand

patentable utilities. Each claimed invention must be shown to meet § 101's utility requirement in order to be patentable; it must provide a specific benefit in currently available form. Providing a single data point among thousands or millions, even if the thousands or millions of data points collectively are useful, does not meet this standard.

The Supreme Court noted that the patent system contemplates a basic quid pro quo: in exchange for the legal right to exclude others from his invention for a period of time, an inventor discloses his invention to the public. See Brenner, 383 U.S. at 534, 148 USPQ at 695. The Brenner Court held that the grant of patent rights to an applicant is justified only by disclosure of an invention with substantial utility – a specific benefit in currently available form. Until the invention has been refined and developed to this point, the Court held, the applicant has not met his side of the bargain, and has not provided a disclosure sufficient to justify a grant of the right to exclude others. See id.

In return for the right to exclude others from using all of these products, Appellants contend that it is enough for them to simply disclose the structure of the claimed polynucleotides, with no disclosure of the encoded protein whatever. Appellant stated in the Brief at page 15 that the biological role or function of an expressed polynucleotide is not required to demonstrate utility, implying that no knowledge of the encoded protein is required for using the nucleic acid. This assertion and the instant disclosure do not satisfy § 101. The basic quid pro quo of the patent system, as interpreted by the Brenner Court, is the grant of a valuable legal right in exchange for a meaningful disclosure of the claimed invention.

Appellants' bare-bones disclosure in this case does not entitle them to the legal right they claim.

It would appear, therefore, that Appellants are using the asserted microarray utility as a stalking horse, to provide a utility that can be asserted for any isolated cDNA, regardless of how little is known about it, which (they hope) will nonetheless serve as a basis for patent protection of all related products and methods and secure for Appellants any value that might become apparent in the future, after they or others have further characterized the claimed products. It was precisely this type of result that the Brenner Court sought to avoid by requiring disclosure of a substantial utility to satisfy § 101. See 148 U.S. at 535-36, 148 USPQ at 696: [The Court was not] "blind to the prospect that what now seems without 'use' may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." Id.

The polynucleotides of the instant claims may indeed prove to be very useful (and valuable), after the in vivo role of the encoded protein is discovered. The work required to confer value on SEQ ID NO:2, however, remains to be done. The instant specification's MRTM-specific disclosure does not justify a grant of patent rights. See Brenner, 383 U.S. at 534, 148 USPQ at 695: "[A] process patent in the chemical field, which has not been developed and pointed to the degree of specific utility, creates a monopoly of knowledge which should be granted only if clearly commanded by the statute. Until the process claim has been reduced to production

of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area. Such a patent may confer power to block off whole areas of scientific development." We consider the Brenner Court's concern about the "power to block off whole areas of scientific development" equally applicable here. Finally, in addition to being contrary to controlling case law, the per se rule that Appellants seek—that any expressed human gene has utility because it can be used in a microarray—would disserve the patent system. In the first place, it is unclear what, if anything, limits the compounds subject to Appellants' proposed rule. Appellants have asserted that this rationale would apply to wholly uncharacterized nucleotide sequences. See the Appeal Brief, pages 8-11. It is also apparent that it applies not only to intact genes, but to fragments of them as small as 10 nucleotides long. See the specification, page 14, second paragraph (Arrays may be prepared and analyzed using methods well known in the art. Oligonucleotides or cDNAs may be used as hybridization probes or targets to monitor the expression level of large number of genes simultaneously).

Nor can the rationale be confined to expressed human genes. Other organisms are of interest for many different reasons, such that gene expression assays could conceivably be used in their research. For example, some organisms are of interest to researchers because they have been historically well-studied (e.g., yeast, Arabidopsis, C. elegans, Drosophila). Other organisms are of interest because they are used as animal models for testing pharmaceuticals (e.g., mice, chimpanzees,

rhesus monkeys, rabbits), or because they are commercially valuable (e.g., pigs, cows, corn, rice, tomatoes), or because they are pests (e.g., fungi such as Fusarium, common weeds like ragweed, insects such as corn borers, nonnative invaders such as zebra mussels, etc.), or because they're pathogens (e.g., Candida, various bacteria, tapeworms, etc.). Under Appellants' proposed rule, every fragment, or oligonucleotide of any gene of any of these organisms—and probably most other organisms—would be found to have patentable utility because it could be attached to a chip and used in "research" to see what happens to expression of that gene under various conditions.

It is apparent, therefore, that Appellants' proposed rule would vitiate the statutory utility requirement for most chemical compounds. If Appellants' reasoning were adopted, it would result in a per se rule that all chemical compounds have utility because each one can be used to do research on others.

Summary

The patent system is based on a balancing of interests. "Patents . . . are meant to encourage invention by rewarding the inventor with the right, limited to a term of years fixed by the patent, to exclude others from the use of his invention. . . . But in rewarding useful invention, the 'rights and welfare of the community must be fairly dealt with and effectually guarded.' Kendall v. Winsor, 21 How. 322, 329 (1859). To that end the prerequisites to obtaining a patent are strictly observed. . . . To begin with, a genuine 'invention' or 'discovery' must be demonstrated 'lest in the constant demand for new appliances the heavy hand of tribute be laid on each slight technological advance

in an art.'" Sears, Roebuck & Co. v. Stiffel Co., 376 U.S. 225, 230, 140 USPQ 524, 527 (1964).

The basic quid pro quo of the patent system requires disclosure of an invention having substantial utility. Appellants' disclosure in this case does not provide a specific benefit in currently available form, and therefore lacks the substantial utility required by 35 U.S.C. § 101. Therefore, for reasons set forth above, Appellants arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility and it is believed that the rejections should be sustained.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 1-6 remain rejected under 112, first paragraph, enablment due to lack of a specific, substantial utility or a well established utility for reasons already of record.

The same arguments and reasons for rejection as set forth under 101 rejection apply here as well.

Further, Appellants' reasoning would also eviscerate the enablement requirement, since "[t]he enablement requirement is met if the description enables any mode of making and using the invention." Johns Hopkins Univ. v. CellPro Inc., 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1714 (Fed. Cir. 1998) (quoting Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991)). If one were to agree with Appellants that any expressed gene, any fragment thereof is useful in a microarray, then one would also have to hold that the specification has taught those skilled in the art one mode of using the invention. Thus, Appellants' rule of

per se utility would also require a corresponding rule of per se enablement. What limit then would remain on patenting of genes and proteins (and potentially any other bioactive compound)? It would seem that under Appellants' rule, a compound would be patentable if it was adequately described in the specification and was not disclosed or suggested in the prior art. This standard, however, is not the one set by Congress, which requires that a patentable invention also be useful and fully enabled, nor is it the standard that has been consistently applied by the courts.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 1-6 remain rejected under 112, first paragraph for lacking a clear written description of a polynucleotide encoding a naturally occurring amino acid sequence having at least 90% sequence identity to SEQ ID NO:1, or a naturally occurring polynucleotide having at least 90% sequence identity to SEQ ID NO:2, for reasons already of record .

Appellant asserts that given SEQ ID NO:1 and 2, and the described chemical, physical and structural features of SEQ ID NO:1, and coupled to what is conventional or well known, one of kill in the art would recognize naturally occurring variants of SEQ ID NO:1, having at least 90% sequence identity to SEQ ID NO:1

The argument is not found to be persuasive. Contrary to Appellant's assertion, the subject matter of the present claims is not defined in terms of the chemical structure of SEQ ID NOs:1 and 2.

The claims as written clearly read on allelic variant polynucleotides of the polynucleotide of SEQ ID NO:2, or allelic polynucleotides encoding variant polypeptides

of the polypeptide of SEQ ID NO:1. No disclosure of the claimed allelic variant polynucleotides beyond the mere mention of variants and allelic sequences is made in the specification. The claims encompass allelic variant polynucleotides encoding polypeptide variants having any type of substitution by nature besides conservative substitution, or deletion by nature at any amino acid, throughout the length of the peptide, provided the changes are within 10% of the sequence identity. The specification does not disclose which amino acid subjected to conservative or non-conservative substitution, or deletion by nature, the type of substitution besides conservative substitution by nature, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous structural polynucleotide variants. No common structural attributes that identify the claimed polynucleotide variants are disclosed. In addition, no common functional attributes that identify the claimed polynucleotide variants are disclosed, because the function of a polypeptide encoded by a polynucleotide could be abolished, even with substitution of only one amino acid of the polypeptide (Burgess et al), and because the function of SEQ ID NO:1 is not known (see the above Utility rejection). The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed naturally occurring polynucleotide variants, SEQ ID NOs:1 and 2 alone are insufficient to describe said variants. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of polynucleotide variants and that Appellant was not

in possession of the naturally occurring variant polynucleotides, and polynucleotides encoding naturally occurring polypeptide variants.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Claims 1-6 remain rejected under 112, first paragraph for lacking enablement for a polynucleotide encoding a naturally-occurring amino acid sequence having at least 90% sequence identity to SEQ ID NO:1, or a naturally occurring polynucleotide having at least 90% sequence identity to SEQ ID NO:2, for reasons already of record.

Appellant asserts that Appellant has previously established utility for the polynucleotide of SEQ ID NO:2 and the polypeptide of SEQ ID NO:1 for reasons discussed previously in this brief. Appellant asserts that the use of the claimed variants in hybridization, amplification, and screening technology to identify and distinguish among SEQ ID NO:2 and related molecules in a sample is fully enabled by the specification.

This argument is not found to be persuasive. Appellant has not taught how to use the invention for the reasons previously set forth for utility. Thus since there is no practical, specific, and substantial uses for the sequence of SEQ ID NO:2, or the predicted encoded SEQ ID NO:1 and variants thereof in diagnosis of disease conditions, or in microarray for reasons set forth in utility rejection, other cited uses of the claimed variants of SEQ ID NO:2 such as hybridization probes, chromosome mapping, amplification, and screening technology to identify and distinguish among SEQ ID NO:2 and related molecules in a sample would not have any practical use either.

Further, no consensus sequences that identify the claimed polynucleotide variants are disclosed, *supra*, and thus one cannot identify and make the claimed variants.

Moreover, identification of the claimed variants, based solely on sequence homology would result in compounds with unknown function, since the unpredictability of utilizing predicted structural determinations to ascertain functional aspects of the protein is demonstrated by Bork and Scott et al, *supra* (see rejection under 101, utilty above), and thus one cannot predict that the claimed naturally occurring variants that are screened by PCR, based solely to 95% identity with SEQ ID NO:or 2 would function as claimed . Bork teaches the pitfalls associated with comparative sequence analysis for predicting protein function and specifically states that conclusions from comparison analysis are often stretched with regard to protein products and specifically cites that most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality. The teaching of Scott et al further confirms the teaching of Bork, wherein Scott et al teach an example of misidentification of the function of a protein based on homology alone, and conclude that it is important to confirm the function of a newly identified gene products even when the database reveal significant homology to proteins of known function.

Thus, one of skill in the art would not know how to use the claimed variants based solely on screening sequences having sequence homology to SEQ ID NO:2, nor how make a polynucleotide encoding a naturally-occurring amino acid sequence having at least 90% sequence identity to SEQ ID NO:1, or a naturally occurring polynucleotide

having at least 90% sequence identity to SEQ ID NO:2, so that they would function as claimed.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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